ATTORNEY DOCKET NO. 22000.0021U2
SERIAL NO. 09/516,310

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#17

In re Application of
Lin and Hawiger

Serial No. 09/516,310
Confirmation No. 3622

Filed: March 1, 2000

For: A NOVEL METHOD FOR IMPORTING BIOLOGICALLY ACTIVE MOLECULES INTO CELLS

Group Art Unit: 1636

Examiner: Loeb, B.

Considered
7/17 2/13/03

DECLARATION OF JOHN S. SUNDSMO, PH.D.

Commissioner for Patents
Washington, D.C. 20231

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1. My name is John S. Sundsmo. I earned a Ph.D. in Microbiology and Immunology with a minor in Biochemistry from the University of Washington in 1973. After post-doctoral research studies in membrane glycolipids and complement system biochemistry I was promoted to the staff in Molecular Immunology at Scripps Clinic and Research Foundation (SCRF, La Jolla, CA) in 1978. Research in my laboratory investigated interrelationships among the complement, coagulation, kinin and fibrinolytic systems and complement inflammatory mediators associated with immune cells in health and disease. I have been continuously involved in the Biotechnology industry since leaving SCRF in 1983. My background has included industrial research and development as relates to both diagnostic and therapeutic biotechnology products, including retroviral gene therapy vectors, wound healing and anti-infective products. I have also practiced intellectual property law, i.e., as a patent agent in law firms. I am a registered United States patent agent (Registration Number 34,446). I presently serve as the Chief Executive Officer for TransCell Therapeutics, Inc., a Tennessee corporation formed to commercialize the

inventions subject in United States Patent Application 09/516,310 and it's related United States and International patents. TransCell Therapeutics, Inc. is the licensee of the 09/516,310 application as well as other scientific advances made by Dr. J. J. Hawiger at Vanderbilt University.

2. On November 27, 2002 I conducted a key word search at the National Library of Medicine internet website (www.ncbi.nlm.nih.gov) where I entered a single word: namely, "hawiger". Fifth among the retrieved document titles I identified the following document: namely,

> Liu, X.Y., D. Robinson, R.A. Veach, D. Liu, S. Timmons, R.D. Collins and J. Hawiger. 2000. Peptide-directed Suppression of a Pro-Inflammatory Cytokine Response. Journal of Biological Chemistry 275 (No. 22): 16774-16778. (The Liu-Hawiger Document).

"Related Articles, Links" was presented as an optional search, and conducting this search I recovered a number of documents.

3. At the National Library of Medicine internet website there existed an opportunity to conduct a subsequent searches for "Related Articles, Links". This additional search, conducted by me, identified documents which I believed may be relevant to an *In re Wands* evaluation of enablement under 35 USC. 112, first paragraph. The documents which I recovered and deemed relevant are identified in Appendix A as Documents #AA through #AL. The possible relevance of each identified Document as post-filing-art is summarized by me in Appendix A as it is attached to the Response to Paper 15.

4. On November 29, 2002 I conducted an additional key word search for articles using the names of certain investigators identified in my first search. I recovered citations to more than 150 documents including a large number of recent review, all published since 1994 and all related to different uses of importation competent peptides to deliver different biologically active molecules.

5. I have reviewed U.S. Patent Application Serial No. 09/516,310 (the '310 application) and also have some familiarity with the contemporary science, both at the time the invention was made, and subsequently. It is my belief that the finding that hydrophobic mammalian signal peptide sequences could mediate both secretion and transduction of peptides and proteins, i.e., the disclosure in the '310 application, was highly unexpected. This most surprising invention solved a major problem for basic and industrial scientists interested in intracellular delivery of biologically active molecules. In particular, until the invention was made it was not possible to routinely introduce peptides and proteins into cells and delivery nucleic acids was unpredictable and at low frequency, particularly in quiescent non-dividing or terminally differentiated cells. Thus, many potential cellular targets of therapy were simply inaccessible.

As proof of commercial utility, among the references collected in my search I found articles originating from laboratories at Bristol-Myers Squibb, Novartis, Astra-Zenica, Biogen and other biotechnology and pharmaceutical companies.

As with most highly innovative discoveries, it has taken some time before scientific acceptance has been forthcoming particularly since, even today, the responsible mechanisms have proved difficult to elucidate. The seeming simplicity of the discovery is what has made it so widely applicable, i.e., knowing that such mechanisms existed was the key discovery that has enabled all subsequent uses. Undue experimentation has not been the case. Instead, because the peptide complexes work so well they are widely used. Today three different well established platforms are known for peptide-mediated transduction: namely, mammalian hydrophobic peptides found in signal sequences; viral amphipathic peptides such as portions of the Tat protein of HIV-1; and, insect homeobox proteins. It is also quite well-established that the "cargoes" carried by these transducing agents can include other peptides, even quite large proteins (e.g., 100kDa), nucleic acids (e.g., plasmids) and oligonucleotides. There are also recent reports that simply attaching an importation competent peptide to adenoviral gene therapy viral vectors may be sufficient to promote entry into mature mammalian cells which were previously off-limits to therapy.

Like the first Edison light bulb that barely glimmered and only lasted a few minutes, now the lights are on and it is to be expected that new generations of

pharmaceutical agents will incorporate the understanding derived from the instant invention. It is to be hoped that, like Edison, innovation will be appreciated and valued.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may jeopardize the validity of the application or any patent issued thereon.

Signed by me this 3rd Day of December in the year 2002,

Signature of John S. Sundsmo, Ph.D.
(Registration No. 34,446)